

### **REMARKS**

Claims 72-82 have been canceled without prejudice. Claims 1, 3-7, 19, 20, 32, 42, and 44 have been amended. Claims 85-92 have been added. Support for the amendments and new claims can be found throughout the specification (e.g., page 12, lines 14-18; page 17, lines 5-9; and Figures 1B, 3A, and 5) and original claims (e.g., claims 2-7). No new matter has been introduced and no new issues have been raised. These amendments have been made solely to expedite allowance of claims. Applicants reserve the right to pursue claims of similar or differing scope in the future.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

#### **Amendments to the Specification and Drawings**

The specification, Figure 1B, and Figure 2B have been amended solely to correct typographic errors. Applicants submit that no new matter is being added.

#### **Election/Restriction**

The Examiner has acknowledged Applicants' election of Group I (claims 1-32 and 42-44) in the Response filed on August 24, 2006.

#### **Information Disclosure Statement**

Applicants note that the Examiner has considered and initialed the Information Disclosure Statements filed on March 1, 2004 and November 25, 2005.

#### **Oath/Declaration**

The Examiner asserts that the declaration is defective for lacking the signature of Glen Larson. Applicants thank the Examiner for the telephone call dated January 16, 2007. Applicants remind the Examiner that Applicants submitted a petition under 37 CFR 1.47 on June 30, 2004 and Applicants' Petition was granted on January 30, 2007.

#### **Claim Objections**

Claims 3-7 and 32 are objected to because they recite a sequence without a sequence identifier. Applicants have amended claims 3-7 and 32 to add a sequence identifier, thereby

obviating the objections. Applicants note that these sequences have been included in the Sequence Listing filed on June 30, 2004.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-2, 8-31, and 42-44 and 27-29 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Specifically, the Office Action asserts that "[c]laims 1, 2, 8-31 and 42-44 are genus claims because the specification (and claims) do not set forth the structure of the multitude of RAGE-LBE's, TNF- $\alpha$  inhibitors, dimerizing polypeptides including amphiphilic polypeptides, purification polypeptides, stabilizing polypeptides, and targeting polypeptides that are encompassed by the invention. Thus, the scope of the claims includes numerous structural variants, and each genus is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the claimed genus from others in the amino acid class are missing from the disclosure." See Office Action, the paragraph bridging pages 4 and 5.

Applicants respectfully submit that the specification sufficiently describes the claimed invention. Applicants point out that where, as in this case, (1) the inventive portion of the subject matter is disclosed and (2) any additional variability within the genus arises due to additional elements that are not part of the inventor's contribution, and when the level of knowledge and skill in the art would allow one skilled in the art to recognize that the applicant was in possession of the genus, the written description cannot be deemed defective. See Written Description Guidelines Training Materials available at, <http://www.uspto.gov/web/offices/pac/writtendesc.pdf> (released March 1, 2000, Example 8, page 35).

In this case, independent claim 1 as amended is directed to a fusion protein comprising a RAGE-LBE and an immunoglobulin element, wherein the RAGE-LBE comprises an amino acid sequence at least 70% identical to an extracellular portion of SEQ ID NO: 7. Independent claim 20 as amended is directed to a fusion protein comprising a RAGE-LBE and a second domain selected from the group consisting of a dimerizing polypeptide, a purification polypeptide, a stabilizing

polypeptide, and a targeting polypeptide, wherein the RAGE-LBE comprises an amino acid sequence at least 70% identical to an extracellular portion of SEQ ID NO: 7.

One of skill in the art would know that the inventive portion of the claimed fusion proteins lies in the unique merging of technological features known in the art. As described above, the specification provides both working examples and sufficient description of the structural and functional characteristics of the genus of the claimed fusion proteins. Thus, a skilled artisan would recognize that Applicants were in possession of the claimed invention.

Applicants further point out that at the time this application was filed, TNF- $\alpha$  inhibitors, dimerizing polypeptides including amphiphilic polypeptides, purification polypeptides, stabilizing polypeptides, and targeting polypeptides were known and understood in the art. In accordance with the written description guidelines and the MPEP, "[i]nformation which is well known in the art need not be described in detail in the specification." Written Description Guidelines for the Examination of Patent Applications, section II, page 1105, column 3; MPEP 2163.

Nonetheless, solely to expedite prosecution of the application, Applicants have amended independent claims 1 and 20 to specify that the RAGE-LBE comprises an amino acid sequence at least 70% identical to an extracellular portion of SEQ ID NO: 7. Support for such amendments can be found throughout the specification. For example, the specification teaches that the term "RAGE-LBE" includes "any extracellular portion of a transmembrane RAGE polypeptide (e.g., soluble RAGE) and fragments thereof that retain the ability to bind a RAGE ligand" (see page 12, lines 14-18). In addition, the specification describes that "[s]ubstitutional variants of the RAGE-LBE also include variants where functionally homologous domains of other proteins are substituted by routine methods for one or more of the above-identified RAGE-LBE domains. Where the variant is a fragment of a particular domain of the RAGE-LBE, it preferably but not necessarily has at least about 70% homology to the corresponding RAGE-LBE domain" (page 17, lines 3-7). Further, the specification provides at least two specific examples of RAGE-LBE, including a mouse RAGE-LBE (SEQ ID NO: 2) as shown in Figure 1B and a human RAGE-LBE (residues 1-344 of SEQ ID NO: 7) as shown in Figures 3A and 7. The mouse RAGE-LBE sequence (SEQ ID NO: 2) is about 77% identical to the human RAGE-LBE sequence (residues 1-344 of SEQ ID NO: 7) (see a sequence alignment enclosed as **Exhibit A**). The mouse RAGE-LBE is a functional homologous domain of

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the human RAGE-LBE as evidenced by its ability to bind to a RAGE ligand (see, e.g., Example 3 on pages 66-68; and Figure 6) and its ability to inhibit collagen-induced arthritis (see, e.g., Example 5 on pages 71-72; and Figure 4).

In light of the ample teachings of the specification, one of skill in the art would readily appreciate that Applicants were in possession of the claimed invention at the time this application was filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections for lack of written description.

Claim Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-2, 8-31, and 42-44 are rejected for lack of enablement. Applicants respectfully traverse these rejections to the extent it is maintained over the claims as amended.

Specifically, the Office Action asserts that "the specification, while being enabling for some RAGE-LBE fusion proteins, does not reasonably provide enablement for RAGE-LBE fusion proteins comprising any TNF- $\alpha$  inhibitor, any dimerizing polypeptide including any amphiphilic polypeptide, any purification polypeptide, any stabilizing polypeptide, or any targeting polypeptide." Office Action, page 5, lines 17-20.

Applicants respectfully disagree. As an initial matter, Applicants point out that the Examiner has mischaracterized the claimed invention. Applicants point out that the fusion protein of claim 1 or 20 does not comprise a TNF- $\alpha$  inhibitor. Instead, a TNF- $\alpha$  inhibitor is included in a pharmaceutical composition such as in claims 43-44.

As mentioned above, Applicants have amended independent claims 1 and 20 to specify the structural and functional features of the RAGE-LBE in the claimed fusion protein. Applicants believe that such amendments render the rejection moot and the specification as filed is enabling for the full scope of the claimed invention. The specification teaches successful production of RAGE-LBE fusion proteins which retain the ability to bind to a RAGE ligand as well as therapeutic applications of these fusion proteins in diseases such as arthritis. The specification provides specific examples of RAGE-LBE fusion proteins (including mouse and human RAGE-LBE-Fc fusions) (see, e.g., Example 3 on pages 66-68; Example 5 on pages 71-72; and Example 6 on 72-73). The

specification provides a representative number of examples, thereby enabling the full scope of the claims.

In sum, Applicants' working examples demonstrate how to make and use the RAGE-LBE fusion proteins. Therapeutic benefits of these RAGE-LBE fusion proteins are also disclosed. Further, the level of skill in the art was high at the time of the filing date of the present application. In fact, the techniques involved in the invention, all of which were well known in the art even before the filing date, are highly reliable and can be readily practiced by a skilled artisan. In view of the knowledge in the art and the ample teachings of the application, one of ordinary skill in the art would readily know how to make and use the claimed method in vivo, without undue experimentation. Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

#### Claim Rejections under 35 U.S.C. § 102(b)

Claims 1-2, 11, and 19 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Morser et al. (U.S. Patent No. 5,864,018). Applicants respectfully traverse the rejections.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1978). Applicants contend that Morser et al. fail to satisfy the criteria for anticipating the present invention.

Independent claim 1 as amended relates to a fusion protein comprising a RAGE-LBE and an immunoglobulin element, wherein the RAGE-LBE comprises an amino acid sequence at least 70% identical to an extracellular portion of SEQ ID NO: 7.

Applicants point out that the term "immunoglobulin element" is defined in the specification to "be any portion of an **immunoglobulin**" (page 17, lines 11-12, emphasis added). The specification also provides examples of the immunoglobulin element, such as "functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain," "the Fc portion of a constant domain," and "the CH1 of the heavy chain or the corresponding region of the light chain" (e.g., page 17, lines 23-26).

Morser et al. describe "a recombinant soluble RAGE/DCC chimeric protein (where the first IG-like domain of RAGE is substituted with the first Ig-like domain of DCC, another Ig-superfamily member)" (column 22, lines 26-28). It appears that the Examiner construes the term "immunoglobulin element" to include the Ig-like domain of DCC. Applicants disagree. First, one of ordinary skill in the art would know that DCC is not an immunoglobulin and the Ig-like domain of DCC is not an immunoglobulin element as recited in claim 1. Second, Applicants wish to draw the Examiner's attention to a recent Federal Circuit decision *Phillips v. AWH Corp.*, 2005 WL 1620331 (Fed. Cir. July 12, 2005). In this opinion, the *en banc* majority holds that when construing patent claims, a court should **consult the specification** and prosecution history to determine if the patentee intended to use particular terms in ways other than their ordinary meaning. Thus, Applicants respectfully submit that the Examiner's claim construction is not consistent with the teachings of the specification.

Applicants submit that Morser et al. do not teach all the elements of independent claim 1 and fail to anticipate claim 1. For the same reasons, Applicants submit that all claims depending from claim 1 are not anticipated by Morser et al. Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

#### Claim Rejections under 35 U.S.C. § 103(a)

Claims 1-2, 8-31, and 42-44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Morser et al. in view of Milne Edwards et al. (U.S. 2002/0102604) and as evidenced by Spriggs et al. (WO 94/10308). Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the following three criteria must be met: (i) there must be some suggestion or motivation to modify the reference or to combine reference teachings, (ii) there must be a reasonable expectation of success of combining the cited references to arrive at the claimed invention, and (iii) the prior art references must teach or suggest each and every limitation of the claimed invention. MPEP 2142-2143.

Applicants submit that the combination of Morser et al. and Milne Edwards et al. as evidenced by Spriggs et al. fails to satisfy the criteria necessary for rendering the claimed invention obvious.

As described above, Morser et al. do not teach or suggest an immunoglobulin element in the RAGE-LBE fusion protein of claim 1. Further, Morser et al. do not teach or suggest a dimerizing polypeptide, a purification polypeptide, a stabilizing polypeptide, or a targeting polypeptide in the RAGE-LBE fusion protein of claim 20.

Milne Edwards et al. disclose production of about 240 different recombinant polypeptides (SEQ ID NOs: 242-482), including fusion proteins which comprise heterologous domains such as Fc or leucine zippers. However, Milne Edwards et al. do not disclose production of any recombinant RAGE polypeptide such as RAGE-LBE fusion proteins as recited in claims 1 and 20. Nor do Milne Edwards et al. teach or suggest an association of the RAGE protein with any disease. Milne Edwards et al. are entirely silent on the RAGE protein as recited in the instant claims.

Even if Milne Edwards et al. is combined with Morser et al., the combination still fails to provide any suggestion or motivation for a skilled artisan to modify Morser's soluble RAGE polypeptides to arrive at the claimed RAGE-LBE fusion proteins. First, there is simply no common connection between these cited disclosures that would have motivated a person skilled in the art to combine these teachings. Second, Morser et al. disclose that the soluble RAGE polypeptides, which lack an immunoglobulin element, a dimerizing polypeptide, a purification polypeptide, a stabilizing polypeptide, or a targeting polypeptide, worked very well as evidenced by the binding assays and therapeutic effects (see, e.g., Examples 2, 3, and 4). In failing to teach or suggest that the soluble RAGE polypeptides need to be further modified, Morser et al. effectively suggest that an additional domain (e.g., an immunoglobulin element, a dimerizing polypeptide, a purification polypeptide, a stabilizing polypeptide, or a targeting polypeptide) is not necessary. In the absence of any evidence that Morser's soluble RAGE polypeptide need to be further modified, one of ordinary skill in the art would have had no motivation to make the RAGE-LBE fusion proteins such as those claimed in the present application.

Applicants further submit that a skilled artisan would not have had a reasonable expectation of success even if, for the sake of argument, these references were properly combined. It was well known in the art that recombinant proteins (e.g., the RAGE-LBE fusion proteins) are unpredictable – they may not be biologically active due to improper tertiary and/or quaternary structure. The cited references, singly or in combination, fail to teach or suggest how to modify the RAGE protein to

arrive at the biologically active RAGE-LBE fusion proteins. As a result, a skilled artisan could not predict that biologically active RAGE-LBE fusion proteins would be successfully made, not to mention that they would be useful for treating a disease. In contrast, the present specification describes successful production and therapeutic application of biologically active RAGE-LBE fusion proteins of the claimed invention.

The Examiner asserts that "[t]he skilled artisan would have been motivated to make these modifications, since both documents teach treatment of Diabetes Mellitus and Alzheimer's disease with the polypeptides of the inventions (co. 19, lines 12 and 16 of the '018 patent and para. 1680 and 1801 of the '604 application). The person of ordinary skill in the art would have had a reasonable expectation of success because both documents teach that the fusion proteins would work (entire document)." See Office Action, page 14, lines 10-15.

Applicants respectfully disagree. A close review of the cited paragraphs in Milne Edwards et al. (the '604 application) reveals that the teachings are solely directed to the polypeptides (e.g., SEQ ID NOs: 242-482) that are unrelated to the RAGE protein. At most, the cited references invite a skilled artisan to combine Morser's soluble RAGE polypeptides with Milne Edwards' polypeptides (e.g., SEQ ID NOs: 242-482) in a composition, rather than an intermolecular combination to arrive at a RAGE-LBE fusion protein as asserted by the Examiner.

In sum, these cited references would not have motivated a person skilled in the art to combine these teachings with a reasonable expectation of success of arriving at the claimed invention. It is the teachings of the present application that provide the motivation to make RAGE-LBE fusion proteins and the reasonable expectation of successfully making and using the RAGE-LBE fusion proteins in the claimed invention.

The Federal Circuit has been clear in establishing the criteria necessary for rendering an invention obvious. "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary



skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

The case law is clear. To render the claimed invention obvious, there must be a motivation to specifically combine Morser et al. and Milne Edwards et al. to arrive at the claimed invention, and this motivation must be grounded in the prior art references themselves, not in Applicants' disclosure. It is simply not enough to identify elements of the claimed invention in individual references or to use Applicants' disclosure as the motivating force for combining the teachings of the prior art.


Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a).

### **CONCLUSION**

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (617) 951-7000. If an additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. **WYTH-P01-002** from which the undersigned is authorized to draw.

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Respectfully submitted,

By 

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Percent Identity

	1	2	
1		77.8	1
2	24.0		2
	1	2	

human RAGE 1-344

mouse RAGE-LBE

Divergence



M A A G T A A G A W V L V L A L W G A V A G G Q N I T A R I G E P L V L S C K G A P K K P P Q Q L E										Majority
10										50
M A A G T A V G A W V L V L S L W G A V V G A Q N I T A R I G E P L V L S C K G A P K K P P Q R L E										human RAGE 1-344 mouse RAGE-LBE
1	M	A	G	T	A	V	G	A	W	
1	M	P	A	G	T	A	R	A	W	mouse RAGE-LBE
W K L N T G R T E A W K V L S P Q G G G P W D S V A R V L P N G S L L L P A V G I V D E G I F R C Q										Majority
60										100
51	W	K	L	N	T	G	R	T	E	human RAGE 1-344 mouse RAGE-LBE
51	W	K	L	N	T	G	R	T	E	
A T N R N G K E V K S N Y R V R V Y Q I P G K P E I V D S A S E L T A G V P N K V G T C V S E G S Y										Majority
110										150
101	A	M	N	R	N	G	K	E	T	human RAGE 1-344 mouse RAGE-LBE
100	A	T	N	R	R	G	K	E	V	
P A G T L S W H L D G K L L V P D G K G V L V K E E T R R H P E T G L F T L Q S E L T V I P A Q G G										Majority
160										200
151	P	A	G	T	L	S	W	H	L	human RAGE 1-344 mouse RAGE-LBE
150	P	A	G	T	L	S	W	H	L	
T P H P T F S C S F S L G L P R H R A L N T A P I Q L R V R E P G P L E G V Q L V V E P E G G A V A										Majority
210										250
201	D	P	R	P	T	F	S	C	S	human RAGE 1-344 mouse RAGE-LBE
200	T	-	H	P	T	F	S	C	S	
P G G T V T L T C A V S A Q P S P Q V H W I K D G A P L P L A P S P V L L L P E V G H E D E G T Y S										Majority
260										300
251	P	G	G	T	V	T	L	T	C	human RAGE 1-344 mouse RAGE-LBE
249	P	G	G	T	V	T	L	T	C	
C V A T H S S H G P Q E S R A V S I S V I E T G D E G P A A G S V G G S G L G T L A L A										Majority
310										340
301	C	V	A	T	H	S	S	H	G	human RAGE 1-344 mouse RAGE-LBE
299	C	V	A	T	H	S	S	H	G	

Decoration 'Decoration #1': Box residues that match the Consensus exactly.